REMARKS

This document responds to the July 5, 2001 Office Action in the above-identified application. A response to the July 5, 2001 Office Action was originally due on October 5, 2001; however, applicant has included herewith a Petition for Two Month Extension of Time extending the original deadline until December 5, 2001, authorizing payment of the required fee of $400.00. Accordingly, this response is timely filed.

Claims 1-21 are pending in the subject application. Applicant has hereinabove amended claim 13. Applicant submits that the amendment of claim 13 raises no issue of new matter. Support for the amendment to claim 13 may be found in original claim 10 and in the specification at page 2, line 27 through page 4, line 9. Accordingly, upon entry of the amendment, claims 1-21 are pending.

Attached hereto is a marked-up version of the changes made to the claims by this amendment, captioned "**PLEASE DO NOT ENTER - Version with markings to show changes made**."

No fee is believed necessary in connection with this amendment.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 13-21 under 35 U.S.C. § 112, second paragraph, as allegedly lacking sufficient antecedent basis for the limitation "Formula 1" in the cited claims.

In response, applicant, in order to advance the prosecution of the subject application, has herein amended claim 13 to incorporate the structure of the compound of Formula I recited in the specification and original claim 10. Applicant submits that the inclusion of the chemical formula of the compound of Formula I in claim 13 provides sufficient antecedent basis for the use of the term "the compound of Formula I" in claims 14-21. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 13-21 under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 103

The Examiner stated that claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Villalobos et al. and Mimori et al. both in view of Ruehl et al.

The Examiner stated that the factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The Examiner stated that the prior art reference of Villalobos disclose of the administration of the heterocyclic-cyclic amine derivative compounds of Formula (1) for improving the memory of Alzheimer's patients, and that Villalobos et al. also disclose that these compounds are

acetylcholinesterase inhibitors, (see section entitled Background of the Invention on page 1 and pages 1-6 under the section entitled Summary of the Invention).

The Examiner stated that Mimori et al. teach of treating the neurological disorder of Alzheimer's disease with inhibitors of acetylcholinesterase, (see abstract).

The Examiner stated that Ruehl et al. teach that:

> "a substantial number of elderly pet dogs are at risk for developing age-related medical and behavior disorders. Veterinary practitioners have long been aware of the occurrence of geriatric behavior problems in pet dogs, such as disturbance of normal sleep-wake cycles and housetraining. Such problems are usually referred to by pet owners and veterinarians as part of the 'old dog syndrome,' or, when severe, as 'senility,' and are incorrectly attributed by pet owners to 'simple aging' or normal aging. [T]hese behavior problems can sometimes be associated with histologic lesions in the brains of affected dogs that are very similar to lesions observed at autopsy in humans with dementia of the Alzheimer's type, (see 1st paragraph, on page 283)."

The Examiner stated that Ruehl et al. further teach that the use of "the term cognitive dysfunction [is] to refer to the age-related or geriatric onset behavior changes, (as cited from 3rd paragraph on page 283), and that the "many behavior changes can be assigned to the following categories: 1) disorientation, 2) decreased or altered social interactions or responsiveness to family members, 3) loss of prior housetraining, 4) disturbances of the sleep/wake cycle, 5) and decreased activity, (see 2nd paragraph on page 284).

The Examiner stated that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The Examiner stated that In this case, the prior art reference of Ruehl et al. equate the Alzheimer's dementia in humans with cognitive dysfunction of animals. Accordingly, it would have been obvious to one having ordinary skill in the art to combine methods of treatment and the pharmaceutical compositions as taught by Villalobos et al. and Mimori et al. along with treating the cognitive dysfunctions in animals.

In response, applicant respectfully traverses the rejection. Applicant submits that the Examiner has failed to make out a prima facie case of obviousness because neither motivation to make applicant's claimed invention nor expectation of success in doing so can be found in the prior art considered as a whole.

Applicant points out that the alleged basis cited by the Examiner for a finding of obviousness ("combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the reference themselves or in the knowledge generally available to one of ordinary skill in the art") as stated is incomplete. Applicant maintains that a finding of obviousness requires that the prior art provide both motivation and a reasonable expectation of success (See, MPEP 2142, 2143).

Applicant admits, as it is plainly true, that the use of acetylcholinesterase (AChE) inhibitors for treating the human disease, Alzheimer's disease (AD), is in the prior art. However, applicant disagrees with the Examiner's conclusion that the prior art teaches or suggests the use of cholinergic agents in animals, for the following reasons:

First, applicant does not agree that Ruehl "equates" cognitive dysfunction in animals with Alzheimer's disease in humans. While Ruehl emphasizes the similarities between AD and cognitive impairment in dogs, even the passage quoted by the Examiner points out that the two are not equal:

> [T]hese behavior problems can sometimes be associated with histologic lesions in the brains of affected dogs that are very similar to lesions observed at autopsy in humans with dementia of the Alzheimer's type" (emphasis added).

Applicant also wishes to point out that other passages in Ruehl make clear that human AD and cognitive problems occurring with aging in dogs are not "equal." For example, Ruehl notes the work of Cummings on comparisons of lesions:

> ...the lesions are very similar, although not identical, to those in the brains of humans with late-stage Alzheimer's disease. The subtle differences in plaque formation between humans and dogs two species sharing the same environment and hence many of the same risk factors, may provide clues as to the cause(s) of CD and brain aging, perhaps ultimately leading to better management or prevention of CD in both species. (Ruehl at 290-291, emphasis added.)

Applicant maintains that "similar" is not "equal," and that it is a mischaracterization of the prior art to infer from Ruehl that a method of treating the human disease AD would be successful in treating cognitive dysfunction in animals. Applicant maintains that because Ruehl fails to provide a reasonable expectation of success, as explained further below, the obviousness rejection must be withdrawn.

Second, applicant notes that a complete reading of Ruehl shows that the prior art teaches away from applicant's invention, removing both motivation and expectation of success.

Applicant submits that Ruehl notes many treatment strategies based on neurotransmitter modulation have been considered, e.g., relating to "dopamine, serotonin, norepinephrine, and especially acetylcholine" (Ruehl at 292), but that a strategy tried with humans – targeting acetylcholine – was not successful, and is not even of interest for use in animals. Ruehl states regarding the cholinergic agent tacrine, that

> "a major effort has met with limited success . . . unfortunately, reported benefits were quite modest and consisted primarily of a slowing of the cognitive decline . . . .we are unaware of any reports of the use of tacrine in dogs" (Ruehl at 293).

Applicant maintains that the disparagement of cholinergic agents constitutes a clear teaching away from applicant's invention – or, alternatively expressed, shows that one of ordinary skill in the art would be neither motivated to make applicant's invention, nor expect it to be successful – which precludes a finding of obviousness. Applicant maintains that it is clear that Ruehl does not suggest the use of cholinergic agents in non-human animals, much less the use of any specific agents such as claimed in applicant's claims 10-21. The only suggestion applicant can find in Ruehl is the use of a dopaminergic agent, L-deprenyl, to treat cognitive dysfunction in dogs. Applicant maintains that the prior art – considered for its full import – fails to provide either the necessary motivation or

the necessary expectation of success to sustain an obviousness rejection. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 103.

CONCLUSION

In view of the above amendments and arguments, applicant respectfully requests that the Examiner reconsider and withdraw the rejections of the pending claims. Applicant believes that this response fully addresses the issues raised by the Examiner; however, if any issues are believed to remain outstanding, the Examiner is invited to telephone applicant's attorney at the number below.

Respectfully submitted,

Date: December 5, 2001

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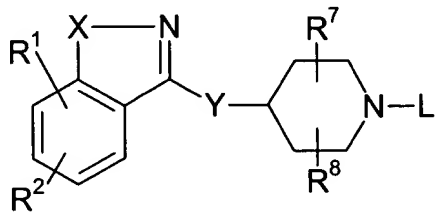
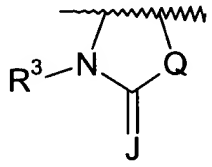
13. (Amended) A pharmaceutical composition for use in the treatment of an age-related behavior disorder in a companion animal comprising a compound of Formula 1:



Formula 1

wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen; (C_1-C_6) alkoxy; benzyloxy; phenoxy; hydroxy; phenyl; benzyl; halo; nitro; cyano; -COR^5; -$COOR^5$; -$CONHR^5$; -NR^5R^6; -NR^5COR^6; -$OCONR^5R^6$; -$NHCOOR^5$; (C_1-C_6) alkyl which may be substituted with from 1 to 3 fluorine atoms; SO_pCH_2-phenyl or SO_p(C_1-C_6) alkyl, wherein p is 0, 1 or 2; pyridylmethyloxy or thienylmethyloxy; 2-oxazolyl; 2-thiazolyl; and benzenesulfonamide; wherein the phenyl moieties of said phenoxy, benzyloxy, phenyl, benzyl and benzenesulfonamide groups, the pyridyl and thienyl moieties of said pyridylmethyloxy or thienylmethyloxy groups, and the oxazolyl and thiazolyl moieties of said 2-oxazolyl and 2-thiazolyl groups may be substituted with 1 or 2 substituents independently selected from the group consisting of halo, (C_1-C_4) alkyl, trifluoromethyl, (C_1-C_4) alkoxy, cyano, nitro and hydroxy;

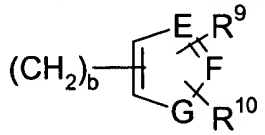
or R^1 and R^2 are attached to adjacent carbon atoms and form, together with the carbon atoms to which they are attached, a group of Formula 2:



Formula 2

wherein R^3 is hydrogen or (C_1-C_6) alkyl; J is oxygen, sulfur or NR^4; R^4 is hydrogen or (C_1-C_4) alkyl; and Q is oxygen, sulfur, NH, $CHCH_3$, $C(CH_3)_2$, -CH=CH-, or $(CH_2)_l$ wherein l is an integer from 1 to 3;
X is oxygen or sulfur;
Y is -$(CH_2)_m$-, -CH=CH$(CH_2)_n$-, -$NR^4(CH_2)_m$-, or -$O(CH_2)_m$-, wherein n is an integer from 0 to 3, and m is an integer from 1 to 3;
R^5 and R^6 are each independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, phenyl, and benzyl, wherein the phenyl moieties of said phenyl and benzyl groups may be substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, chloro, bromo, iodo, (C_1-C_4) alkyl, trifluoromethyl, (C_1-C_4) alkoxy, cyano, nitro and hydroxy; or

NR^5R^6 together form a 4 or 5 membered ring wherein one atom of the ring is nitrogen and the others are carbon, oxygen or nitrogen; or NR^5COR^6 together form a 4 or 5 membered lactam ring;
L is phenyl, phenyl-(C_1-C_6) alkyl, cinnamyl or pyridylmethyl, wherein the phenyl moieties of said phenyl and phenyl-(C_1-C_6) alkyl may be substituted with 1 to 3 substituents independently selected from the group consisting of (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_4) alkoxycarbonyl, (C_1-C_6) alkylcarbonyl, -$OCONR^5R^6$, -$NHCOOR^5$, and halo; or L is a group of Formula 3:



Formula 3

wherein b is an integer from 1 to 4; R^9 and R^{10} are independently selected from the group consisting of hydrogen, (C_1-C_4) alkyl, halo, and phenyl; E and F are independently -CH- or nitrogen; and G is oxygen, sulfur or NR^4, with the proviso that when E and F are both nitrogen, one of R^9 and R^{10} is absent; and
R^7 and R^8 are independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxycarbonyl, (C_1-C_6) alkylcarbonyl, and (C_1-C_6) alkoxy, with the proviso that said (C_1-C_6) alkoxy is not attached to a carbon that is adjacent to a nitrogen;
or a pharmaceutically acceptable salt of solvate thereof, and a pharmaceutically acceptable carrier.